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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,197	07/31/2001	Rosanne M. Crooke	ISPH-0593	3965

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MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER

MCGARRY, SEAN

ART UNIT	PAPER NUMBER
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1635

13

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N

09/919,197

Applicant(s)

CROOKE ET AL.

Examiner

Sean R McGarry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-15 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-15 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Claims 15 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of a nucleic acid encoding short heterodimer partner-1 via an antisense oligonucleotide targeted to SEQ ID NO: 3, does not reasonably provide enablement for the in vivo/ whole animal application of those antisense oligonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is repeated for the same reasons of record set forth in the Official Action mailed 12/18/02.

The instant invention is broadly drawn to the treatment of a whole animal in the treatment or prophylaxis of various diseases or conditions that may be associated with short heterodimer partner-1. The diseases and conditions include abnormal lipid metabolism, abnormal cholesterol metabolism, atherosclerosis, and cardiovascular disease, for example.

The instant specification shows, in examples 15-17, the inhibition of short heterodimer partner-1 in hepatocytes. The specification provides general guidance known in the art for formulations and modifications of antisense oligonucleotides and general strategies for antisense based therapy.

The instant specification, however, fails to provide one in the art adequate guidance or examples that show by correlation the practice of the instant invention such

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that one could practice the invention without undue trial and error experimentation, for example. The instant specification does not provide any specific guidance one would follow in the treatment or prophylaxis of various diseases or conditions associated with short heterodimer partner-1. The diseases and conditions embraced in the instant claims include abnormal lipid metabolism, abnormal cholesterol metabolism, atherosclerosis, and cardiovascular disease, for example. The instant specification does not provide specific guidance for these generic disease/condition categories and provides no guidance for any specific disease that may be embraced within these generic categories, for example. The instant specification shows, in Examples 15-17, the inhibition of short heterodimer partner-1 in hepatocytes but does not explain or show how the inhibition of heterodimer partner-1 inhibition in hepatocytes would correlate to the treatment of cardiovascular disease or cholesterol metabolism, for example. Furthermore, Examples 15-17 do not provide any evidence or discussion of what effects the inhibition of short heterodimer partner-1 had on the hepatocytes and how such effects would correlate with the treatment or prophylaxis of the recited diseases or conditions, for example.

One in the art would require more specific guidance than that provided in the instant specification since the art of nucleic acid based therapy is an unpredictable art. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally

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anticipated, and their ability to eliminate the function of a single gene has never been proven.”; “[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest.”; “[h]owever, their unpredictability confounds research applications of nucleic acid reagents.”; “[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.”; “Years of investigation can be required to figure out what an ‘antisense’ molecule is actually doing. . . .”; “Because knowledge of their underlying mechanism is typically lacking, non-antisense effects muddy the waters.”; “because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known.”; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range.”; “[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells.”; “[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary

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sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible.”; and, “[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*.”

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert “[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive.” It is also stated “[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy.” It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: “ [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process”

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(page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . . [i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

In view of the state of the art and that which has not been taught in the instant specification, one in the art would be required to perform undue trial and error experimentation to practice the instant invention. One in the art would need to overcome those general obstacles exemplified in the cited art where the quantity of undue trial and error experimentation would include de novo experimentation to overcome these obstacles for the treatment and/or prophylaxis of each specific disease embraced in applicants claims, where the instant specification does not provide any specific guidance for these diseases or conditions and since the prior art has shown that one can not rely on in vitro data to indicate success in an in vivo environment, for example.

Applicant's arguments filed 4/23/03 have been fully considered but they are not persuasive. Applicant has amended the claims to read "*in vivo*" and assert that this overcomes the rejection of record. It is noted that the rejection of record is based primarily on the use of antisense oligonucleotides in an *in vivo* environment and the rejection of claim 15 is maintained for those same reasons.

Claims 1, 2, and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slunder et al [Developmental Biology Vol. 184: 303-319, 1997] , Nishigori et al [PNAS Vol. 98(2): 575-580], Baracchini et al [US 5,801,154], Bennett et al [5,998,148], Weintraub [Scientific American, January, 1990, pages 40-46], and applicants admission of GenBank accession number L76571 incorporated as SEQ ID NO:3, at page 86.

The claimed invention is antisense compounds that are 8-50 nucleobases in length that are targeted to SEQ ID NO: 3 and which inhibit the expression of short heterodimer partner-1 expression. The invention includes antisense oligonucleotides and further comprises modifications and formulations of these antisense oligonucleotides and compounds as recited in the claims 4-13. The invention also includes a method of inhibiting short heterodimer partner-1 expression in cells via such compounds.

Slunder et al have taught the nhr-2 gene [equivalent of short heterodimer partner-1, see page 3 of the instant specification, for example]. Slunder et al have

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taught the inhibition of the *C. elegans* *nhr-2* with antisense RNA in the study of *nhr-2* function (see abstract and page 309 and 316-317, for example).

Nishigori et al. Have taught that mutations in short heterodimer partner-1 in Japanese are associated with mild obesity. It is taught at page 579, for example, that antagonists of short heterodimer partner-1 could have a significant effect on body weight and assert that such antagonists should be identified and characterized.

Weintraub has taught that antisense oligonucleotides will eventually be used in the treatment of certain diseases but that they are valuable research tools.

Bennett et al have taught general targeting guidelines at columns 3-4, for example. It has been taught to target 5'untranslated regions, start codons, coding regions, and 3'untranslated regions of a desired target, for example. It has been taught in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics, for example. At column 5 it has been taught that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. At columns 6-7 it has been taught preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, for example. At columns 7-8 it has been taught that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. It has also been taught to modify nucleobases in antisense oligonucleotides at column 8-9 which includes the teaching of 5-methyl cytosine and at column 10 it has been taught chimeric antisense oligonucleotides. All of the above referred to modification are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example.

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At columns 10-24, for example it has been taught numerous "carriers" for antisense oligonucleotides. In table I it has been taught the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification).

Baracchini et al have taught, at column 6 for example, that antisense oligonucleotides can be used for research purposes and have also taught at column 6 that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

One in the art would have been motivated to make antisense oligonucleotides of 8-50 nucleobases in length targeted to short heterodimer partner-1 [SEQ ID NO: 3] since that art has shown the inhibition of a short heterodimer partner-1 nucleic acid via

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an antisense mRNA and since that art has linked human mutant short heterodimer partner-1 expression to mild obesity. One would have been motivated since that art has shown the use of antisense in the determination of function of a short heterodimer partner-1 and since the gene has been linked with obesity for example. One in the art at the time of invention would clearly have been interested in developing compounds that would be useful in the study of short heterodimer partner-1 where the art has shown that use of antisense for this gene and since the art has shown that the gene is linked to a disease that may be treatable with an antagonist of short heterodimer partner-1 expression which is how and antisense could function, for example. Bennett and Baracchini et al have also indicated that antisense functions as a tool for gene study and further have taught the benefits of modification of antisense oligonucleotides and the benefits of formulations for antisense delivery to cells for example. One in the art would clearly have had an expectation of success since the prior art has shown the success of inhibiting short heterodimer partner-1 expression via antisense and since Bennett et al and Baracchini et al have both shown the successful use of antisense in cell by following their general rules for antisense design, for example. The targeting of SEQ ID NO: would have been an obvious choice since it was a known and published sequence for human short heterodimer partner-1.

The invention as a whole would therefore have been prima facie obvious to one in the art at the time the invention was made.

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Applicant's arguments filed 4/23/03 have been fully considered but they are not persuasive.

Applicant argues that the nhr-2 gene of Slunder et al is not an equivalent of a short heterodimer protein -1 of the instant invention. It is noted that it was from applicants specification that the nhr-2 gene was indicated as an equivalent since the specification asserts that heterodimer partner-1 is also known as nuclear hormone receptor, for example (see page 3 of the specification). However, even if the nhr-2 is not an equivalent of the instant heterodimer partner-1 of the instant rejection it is clearly a member of the same class of receptors and Slunder et al have clearly shown the use of antisense for the study of function of a member of the same class of proteins, for example. Applicant then asserts that Nishigori et al have merely taught that SHP could be regulated by "yet-unidentified ligands" at page 479, col.2. First, it is assumed that applicant means page 579 of Nishigori et al. It is noted that the full context of Nishigori's conclusion further asserts that "and the results described here suggest that such SHP agonists or antagonists could have a significant effect on body weight. [a]ccordingly, identification and characterization of possible ligands should provide new insight into mechanisms of fetal growth and energy expenditure." Applicant argues that the combination of references merely provides a wish list and provides a bald suggestion that it is "obvious to try" to make antisense oligonucleotides. Applicant also asserts that only portions of the references were ignored and that the only motivation comes from applicants disclosure. It is noted that the combination of references clearly provides a motivation to make antisense and also makes it clear that one in the art

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would have at least a reasonable expectation of success in making antisense to heterodimer partner -1. The Slunder reference as a whole, at least, provides a motivation to use antisense in the determination of gene function in nuclear hormone receptors and also shows success in doing so, for example. The Nishigori et al reference provides motivation to find inhibitors of SHP-1 since "...SHP agonists or antagonists could have a significant effect on body weight. [a]ccordingly, identification and characterization of possible ligands should provide new insight into mechanisms of fetal growth and energy expenditure". Weintraub et al has taught that antisense is a desirable method for determining gene function. Bennett et al and Baracchini et al have both taught, in general, how to make antisense, have taught that antisense can be used in research and have shown that based on those teachings antisense to any particular target can be expected. At the very least the combination of references has taught that antisense has been successfully used to study nuclear hormone receptor function (heterodimer protein-1 is a member of the nuclear hormone receptor class of genes) and that one in the art should find antagonists of heterodimer protein-1 to find new insights into fetal growth and energy use. The art also teaches that antisense, in general, is applicable to the study of any gene and the art has provided clear guidance on how to make and use antisense to any target and the art has also shown that by following the teachings of the art one can use antisense in the study of gene function, for example.

The following prior art is made of record and not relied upon and is not considered pertinent to applicant's disclosure. Bennett et al [US 6,121,047] is drawn to antisense targeted to SHP-1. The SHP-1 disclosed in that application is designating the gene **Src** homology region 2-domain phosphatase that is a cytosolic tyrosine phosphatase. The SHP-1 referred to in the instant specification (see page 3) is short heterodimer partner-1 expression.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

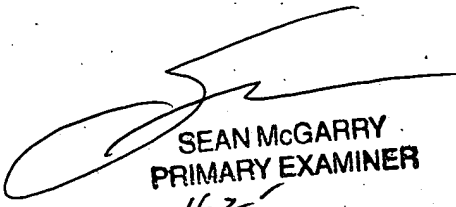
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
June 23, 2003


SEAN MCGARRY
PRIMARY EXAMINER
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